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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,878	02/02/2006	Andries Van Es	0807620.00111	9964

545 7590 04/28/2011

IP Patent Docketing
K&L GATES LLP
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EXAMINER	
TSAY, MARSHA M	
ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
04/28/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/566,878	VAN ES ET AL.	
	Examiner	Art Unit	
	Marsha Tsay	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,9-28 and 30-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,9-28 and 30-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 18, 2010 has been entered.

Applicants' arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 2, 8, 29 are canceled. Claims 1, 3-7, 9-28, 30-32 are currently under examination.

Priority: The request for priority to EPO 03077451.7, filed August 5, 2003, is acknowledged.

Objections and Rejections

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-7, 9-28, and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al. (WO 0134801; IDS 04.10.06, previously cited) in view of Wang (Wang 2000 International Journal of Pharmaceutics 203: 1-60; previously cited) as evidenced by Cortesi et

al. (1998 Biomaterials 19: 1641-1649; previously cited). Cortesi et al. has been used as evidence that mammalian gelatins have a glass transition temperature of 180-200º C (p. 1647).

Chang et al. disclose vaccines comprising recombinant gelatin and a method of producing such vaccines. Chang et al. disclose a dried vaccine formulation comprising recombinant gelatin (p. 85 line 9, p. 86 line 29; claim 1) or lyophilized vaccines comprising using recombinant gelatin as a stabilizer (p. 61 lines 35-38; claim 1). Accordingly, the recombinant gelatin is essentially a polymer that stabilizes the pharmaceutical formulation and should have characteristics similar to an animal-source gelatin, i.e., MW, melting temperature, thermal stability etc. (p. 65 lines 5-6, 21-33). Therefore, the use of recombinant gelatin offers the advantage of reducing the risk of unwanted immune responses from the gelatin itself (p. 59 lines 12-19). Chang et al. disclose the recombinant gelatin can be derived from a human sequence or animal sources (p. 59 lines 16-19), wherein the term "derivative" encompasses those molecules containing at least one structural and/or functional characteristic of the molecule from which it is derived (p. 15 lines 11-15). It is known that gelatin comprises consecutive Gly-Xaa-Yaa triplets. The recombinant gelatin can have a molecular weight range between 0 kDa to 350 kDa, for example 0 to 60 kDa (p. 64 liness 19-21, 85 lines 22-26; claim 3). Chang et al. also disclose a method of producing a composition comprising a vaccine and recombinant gelatin (p. 88 lines 25-32; claim 9). In a non-limiting example, i.e. Example 4, Chang et al. disclose the expression of a non-hydroxylated recombinant human gelatin, which would therefore be free of a helical structure (p. 73 lines 5-10; claims 1, 6-7, 15-20). Further, Chang et al. disclose the recombinant gelatins can possess particular ranges of molecular weights (p. 63 lines 30-32, example 1; claims 5, 12-14). Chang et al. do not teach a glass transition temperature for gelatin.

Wang discloses that lyophilized proteins need stabilization in the solid state to survive long-term storage as pharmaceuticals (p. 25 col. 2). Accordingly, the glass transition temperature of protein formulations is considered to be one of the major determinants of protein stability (p. 28 col. 2). Wang discloses that generally the higher the glass transition temperature of the polymer in said formulation, the more stable the protein formulation; therefore, the glass transition temperature may be used as a guiding parameter to screen protein stabilizers, i.e. by DSC (differential scanning calorimetry) (p. 28 col. 2 to p. 29 col. 1). In Tables 1 (p. 19) and 2 (p. 39), Wang discloses gelatin can be used as a polymer to stabilize lyophilized pharmaceuticals.

It is known in the art that mammalian gelatins have a glass transition temperature of 180-200° C (evidenced by Cortesi et al., p. 1647)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Chang et al. by producing a lyophilized composition comprising a protein drug and a recombinant gelatin such that said recombinant gelatin has a polypeptide sequence that is identical to a region of a native human collagen sequence having a high glass transition temperature (as suggested by Wang), where said recombinant gelatin has the same functional and/or structural characteristics as said native gelatin, i.e. having a glass transition temperature of 200° C (as evidenced by Cortesi et al.) (claims 1, 3-7, 9-28, 30-32). Since Chang et al. disclose that recombinant gelatin comprising a native collagen sequence can minimize immune response and can be used as a stabilizer for improving thermal stability in lyophilized vaccine formulations, and Wang further discloses that polymers having a high glass transition temperature provide the most stability to a protein formulation, one of ordinary skill

would be motivated to produce a recombinant gelatin that has a high glass transition temperature at least equivalent to native gelatin (i.e. 200° C) or higher than 200° C since Wang discloses that generally the higher the glass transition temperature of a polymer determined by DSC, the more stability it imparts on a lyophilized pharmaceutical composition.

Regarding the limitations of claims 24 and 31, i.e. selecting a region of the amino acid sequence of a native collagen having a calculated average glass transition temperature higher than the calculated average glass transition temperature of the complete native collagen by at least 10 degrees Celsius, it should be noted that since gelatin is hydrolyzed collagen, its amino acid sequence would only contain a region of the complete amino acid sequence of native collagen and in view of Wang, it would be reasonable for one of ordinary skill to select a gelatin having a glass transition temperature at least equivalent to native gelatin (i.e. 200 ° C) or higher than 200° C, which would mean the glass transition temperature is at least 10 degrees Celsius greater than the complete native collagen.

The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969). In this instance, the motivation would be to produce a recombinant gelatin sequence having a mammalian gelatin sequence that also has a glass transition temperature at least equivalent to native gelatin such that said recombinant gelatin can be used to make the most stable lyophilized protein formulation.

In their remarks, Applicants assert that **(1)** claim 1 recites that the glass transition temperature is calculated using a mathematical formula, and certain amino acid values. Furthermore, Applicant has discovered that the stability of a lyophilized composition comprising a recombinant or synthetic gelatin-like polypeptide stabilizer relates to the calculated glass transition temperature of the polypeptide which was not known to the art prior to Applicants' invention. Chang et al. do not teach that Chang et al.'s recombinant gelatin can have characteristics similar to those of a native human collagen sequence. Rather Chang et al. disclose that their invention provides, in one embodiment, recombinant gelatin with characteristics similar to hydrolyzed animal-source gelatin..." See Chang et al. p. 65 lines 21-23. Also, Wang et al. do not appear to describe or suggest that a calculated glass transition temperature of a polypeptide would be related to the stability of a lyophilized composition comprising the polypeptide. None of the cited art, Chang et al., Wang et al., or Cortesi et al. appear to disclose a recombinant or synthetic gelatin-like polypeptide having a calculated glass transition temperature of higher than 180 degrees Celsius. Nor do any of the references appear to disclose how such a polypeptide can be made. **(2)** The glass transition temperature in Cortesi et al. appears to be an experimentally determined glass transition temperature. In contrast, Applicants' claim 1 recites a calculated glass transition temperature not an experimentally determined glass transition temperature. The Office does not appear to distinguish between an experimentally determined glass transition temperature and a calculated glass transition temperature. **(3)** In any event, Cortesi et al. do not appear to be pertinent to the patentability of Applicants' claim 1 because Cortesi et al. appear to relate to whole gelatins and cross-linked gelatins, not to hydrolyzed gelatins. Therefore, a person of ordinary skill in the art would not be

motivated to combine Cortesi et al.'s teaching with that of Chang et al., even in light of Wang teachings regarding the role of glass transition temperature in the stability of lyophilized solid protein pharmaceuticals, because, as already pointed out herein, Chang et al. describes recombinant gelatin "with characteristics similar to those of hydrolyzed animal-source gelatin..." (emphasis added), not animal-source gelatin per se. See Chang et al. page 65, lines 21-23 relied upon in the Office action. Furthermore, as described in Applicant's specification, at page 3, lines 29-31, in general, native collagen polypeptides have a calculated glass transition temperature of about 170° C, or less. Nothing in Cortesi et al., or on the record herein, appears to suggest that the mammalian gelatins referenced in Cortesi et al. will have a calculated glass transition temperature greater than 170° C. **(4)** In addition, nothing in Cortesi et al. appears to suggest that Cortesi et al.'s mammalian gelatins that "show an intense glass transition temperature located around 180-200° C" would have a molecular weight between 3,000 Dalton and 80,000 Dalton, as is recited in applicant's claim 1. **(5)** Applicants provide further arguments regarding a calculated glass transition temperature (p. 17-20 of Applicants' remarks received February 18, 2010). **(6)** The Office action does not appear to show how the limitation that the selected region is to have a calculated average glass transition temperature higher than that of the native collagen by at least 10 degrees Celsius, as recited in claim 24, is met by the art of record.

Applicant's arguments have been fully considered but they are not persuasive.

(1) Response: Firstly, it should be noted that instant claim 1 is drawn to a product. The calculated glass transition temperature is a process by which the glass transition temperature is obtained. The MPEP states that "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The

patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted). MPEP 2113.

In this instance, there is no distinction as to how an experimentally determined glass transition temperature is different than a calculated temperature because regardless of how said temperature is determined or arrived at, it is still a temperature of greater than 180° C.

Regarding Wang, while Wang does not explicitly describe or suggest that a calculated glass transition temperature of a polypeptide would be related to the stability of a lyophilized composition comprising the polypeptide, it should be noted that Wang does disclose that the glass transition temperature of protein formulations is considered to be one of the major determinants of protein stability (p. 28 col. 2) and that generally the higher the glass transition temperature of the polymer in said formulation, the more stable the protein formulation is.

Since as noted above, there is no distinction as to how an experimentally determined glass transition temperature is different than a calculated temperature because regardless of how said temperature is determined or arrived at, and the state of the art (Chang et al., Wang, and Cortesi et al.) is such that it is known that recombinant gelatins having characteristics of native mammalian gelatins can be used as a stabilizer in protein formulations and that the higher the glass transition temperature of the stabilizer (i.e. in this instance, gelatin) is, the more stable the protein formulation will be and further, since it is known that mammalian gelatins have a glass transition temperature of 180-200° C, it would be reasonable for one of ordinary skill to incorporate a recombinant mammalian gelatin having a glass transition temperature of at least

180° C into a lyophilized composition comprising a physiologically active substance (i.e. a protein, vaccine, etc.).

(2) **Response**: See the response of (1).

Specifically, instant claim 1 is drawn to a product. The calculated glass transition temperature is a process by which the glass transition temperature is obtained. The MPEP states that "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted). MPEP 2113.

In this instance, there is no distinction as to how an experimentally determined glass transition temperature is different than a calculated temperature because regardless of how said temperature is determined or arrived at, it is still a temperature of greater than 180° C.

(3) **Response**: Regarding Applicants' remarks that Chang et al. describe recombinant gelatin "with characteristics similar to those of hvdrolvzed animal-source gelatin..." (emphasis added), not animal-source gelatin per se, it should be noted that the animal-source gelatin is still a polymer, whether it is hydrolyzed or non-hydrolyzed. Therefore, since it was known in the art (Chang et al., Wang, and Cortesi et al.) that recombinant gelatins (i.e. a polymer) having characteristics of native mammalian gelatins can be used as a stabilizer in protein formulations and that the higher the glass transition temperature of the stabilizer (i.e. in this instance, gelatin) is, the more stable the protein formulation will be and further, since it is known that mammalian

gelatins have a glass transition temperature of 180-200° C, it would be reasonable for one of ordinary skill to incorporate a recombinant mammalian gelatin having a glass transition temperature of at least 180° C into a lyophilized composition comprising a physiologically active substance (i.e. a protein, vaccine, etc.).

Regarding Applicants' remarks on how Cortesi et al. do not suggest that the mammalian gelatins referenced in Cortesi et al. have a calculated glass transition temperature greater than 170° C, see the response of (1) and (2) regarding there is no distinction as to how an experimentally determined glass transition temperature is different than a calculated temperature because regardless of how said temperature is determined or arrived at, it is still a temperature of greater than 180° C.

(**4**) **Response**: Applicants are reminded that the references cited are all considered as 103(a) references. Therefore, the deficiency of Cortesi et al. to disclose the molecular weights recited in instant claim 1 is remedied by the Chang et al. reference.

(**5**) **Response**: See the response of (1), (2), (3), and (4).

(**6**) **Response**: Claim 24 does not identify the characteristics of the selected region except that it is identical or essentially similar to a selected region of the amino acid sequence of a native collagen. Therefore, said selected region could still be the complete amino acid sequence of native collagen. As noted above, Cortesi et al. disclose that mammalian gelatins have a glass transition temperature of 180-200° C, which therefore, meets the scope of instant claims 1 and 24, when used with Chang et al. and Wang et al.

At least for these reasons, the 103(a) rejection is maintained.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha Tsay whose telephone number is (571)272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marsha Tsay/
Primary Examiner, Art Unit 1656

April 19, 2011